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Antiemetic Activity of Fosaprepitant as a Rescue Agent in Patients with Postoperative Nausea and Vomiting after Orthopedic Surgery

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Abstract

Background: Postoperative Nausea and Vomiting (PONV) is a common postoperative complication in the orthopedic surgical setting which may result in significant consequences. Many agents exist for PONV prophylaxis but rescue options remain a big challenge. Fosaprepitant has been studied in PONV prophylaxis but 'evidence for use of Neurokinin-1 Receptor Antagonists (NK-1 RA) for PONV rescue is lacking. Assessing fosaprepitant as a rescue agent for PONV in the orthopedic surgical population was warranted.

Methods: In this single center retrospective chart review, the antiemetic activity of fosaprepitant (selective NK1 receptor antagonist) was investigated as a rescue agent for PONV in patients undergoing orthopedic surgery. Based on the institutional protocol, fosaprepitant was only utilized in patients who experienced PONV with an existing history of PONV or when 2 antiemetic agents were exhausted with no success in the postoperative period. Chart reviews, progress notes, electronic message requests, pyxis medication removal reports and clinical interventions were utilized to assess emesis relief. The primary outcome was to assess fosaprepitant's effect as a rescue agent for PONV in the orthopedic surgical setting.

Results: A total of 383 patients (over a 12-month period) were approved based on the hospital protocol to receive fosaprepitant as a rescue agent. Out of the 383 patients, 286 had relief with fosaprepitant, with 196 patients not requiring further antiemetic therapy. Patient demographics, anesthesia type, additional medications and surgical types were all assessed thoroughly. Three of the surgical types showed the potential significance for fosaprepitant PONV relief: Sports management and shoulder 81% (p=0.0012), adult reconstruction and joint replacement 78% (<0.0001), Spine 66% (p=0.015).

Conclusion: The data shows there may be potential for utilizing fosaprepitant as a rescue agent for PONV in the orthopedic setting. A bigger study with a larger sample size is encouraged.

Keywords: Vomiting; Nausea; PONV; Antiemetics; Pharmacology; Fosaprepitant; Surgery; Orthopedics

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Background

Nausea and vomiting are two of the most common adverse events in the postoperative period with an estimated incidence of 30% in the general surgical population and as high as 80% in high-risk cohorts [1]. PONV is associated with significant patient dissatisfaction, significantly longer stay in the Post-Anesthesia Care Unit (PACU), unanticipated hospital admission, and increased health care costs [2-6].

Several medications are used for the prophylaxis of PONV, including glucocorticoids, 5-HT3 Receptor Antagonists (5-HT3 RA), Neurokinin-1 Receptor Antagonists (NK-1 RA) and antihistamines. Combination therapy appears to be more efficacious for prophylaxis in patients who are at high risk of PONV [7]. Tools such as the Apfel Score can help stratify patients at risk of PONV and who would benefit from prophylactic antiemetics. The Apfel simplified risk score is an assessment tool that assesses patient risk for PONV based on the four most important factors. These include, the female gender, history of motion sickness or PONV, non-smoking status, and postoperative opioid use. Apfel scores range from 0 to 4, in which the higher score is associated with a greater 24-h risk of PONV [1]. Recommendations are to consider >2 anti-emetic agents as prophylaxis in high-risk

patients with >2 risk factors. If prophylaxis fails it is recommended to use an antiemetic that is of a different class from the prophylactic treatment [8]. As such, it is important to understand the relative efficacy of different antiemetic drug classes when used as treatment for break-through PONV. The 5-HT3 RA drug class has had large scale studies done to provide evidence in their use as treatment for established PONV [9]. NK-1 RAs, on the other hand, do not have a wealth of data supporting their use as rescue therapy. One NK-1 RA in particular, fosaprepitant, has limited evidence supporting its use as rescue therapy for established PONV. Fosaprepitant is the prodrug formulation of aprepitant. It is administered intravenously, has a longer half-life than the aprepitant formulation, and is a highly selective NK-1 receptor antagonist. The active metabolite, aprepitant, elicits its pharmacodynamic activity by inhibiting the substance P/ neurokinin 1 receptor, in addition to augmenting the antiemetic activity of the 5-HT3 RAs and corticosteroid activity. The short onset is particularly important as a rescue agent as patients with PONV require immediate relief [10]. The immediate relief can also be helpful in preventing further post-operative complications and prolonged length of stay.

Although 'evidence for use of NK1RAs for PONV rescue is lacking, NK-1 inhibitors have shown to be beneficial at preventing PONV [11]. One systematic review and meta-analysis suggest that NK-1 receptor antagonists, alone or in combination with other drugs, are superior to 5-HT3 receptor antagonists in preventing nausea and vomiting 0 to 24 and 0 to 48 h postoperatively [12]. Another systemic review and meta-analysis concluded that aprepitant reduced the incidence of vomiting when compared to conventional antiemetics [13]. It should be noted that aprepitant has been found to be more effective than ondansetron in preventing PONV in the perioperative period [14]. Dosed alone or in combination with other antiemetics, aprepitant has shown tremendous relief of symptoms and for a prolonged period of time. The novel drug has addressed both acute and delayed onset of nausea and vomiting, which is very useful in the postoperative population because it decreases the need for rescue doses later in the postoperative period [15]. In gynecologic abdominal surgery with patient-controlled epidural analgesia, fosaprepitant more effectively decreased the incidence of vomiting when compared to ondansetron [16]. When studying PONV after craniotomy, fosaprepitant was more effective than droperidol in preventing vomiting over a 72-h period and more effective than ondansetron in achieving complete response by effectively lowering incidence of vomiting at the 24-h and 48-h time points [17,18]. Both aprepitant and fosaprepitant are considered to be effective for Chemotherapy-Induced Nausea and Vomiting (CINV), and their use has been approved for the prevention CINV by the US Food and Drug Administration (FDA) [19]. The use of aprepitant for the prevention of PONV has also been approved by the FDA, but fosaprepitant has not yet gained this approval.

The efficacy of oral aprepitant as rescue therapy was studied in a phase 2 study investigating it's use for patients with breakthrough Chemotherapy-Induced Nausea and Vomiting (CINV). In this study, aprepitant exhibited some potential in treating established (CINV), although the data did not reach expected outcome measures set by the investigators [20]. In regards to fosaprepitant, there are case studies exist which illustrate the use of fosaprepitant for the treatment of refractory postoperative nausea and vomiting [21].

There is data suggesting that a drug acting at a different receptor site may be beneficial as a rescue agent for PONV in patients who failed prophylaxis with an antiemetic agent compared with a repeat dose of the same agent used for prophylaxis [22]. As such it is warranted that a larger study investigating the efficacy of fosaprepitant in patients with established PONV would help to further provide evidence in supporting NK-1 RAs as an effective rescue therapy treatment option. In doing so, clinicians can confidently utilize the unique mechanism of action of NK-1 RAs to treat established PONV that has failed prophylactic therapies. The aim of this retrospective chart review was to evaluate the efficacy of fosaprepitant in the treatment of established emesis after various orthopedic surgeries.

Methods

In this single center retrospective chart review, we analyzed the efficacy of fosaprepitant when used as rescue treatment for PONV in adults. The Hospital for Special Surgery is an orthopedic center of excellence and top performing orthopedic surgical hospital located in New York City. The patients included in this study were those experiencing PONV who either failed at least two rescue agents or have a history of PONV in the past. Patients who received oral aprepitant prior to surgery for prophylaxis, or were on strong CYP3A4 inhibitors/inducers were excluded from the study. Surgical type, anesthesia type (general *vs.* regional) and patient demographics (age and sex) were considered and fully evaluated when analyzing the results.

The groups evaluated are concluded to be patients with and without emesis relief. Relief was defined as no vomiting and no use of an antiemetic medication for at least 8 h after fosaprepitant administration. This time frame was strategically chosen to compare with the average relief of the "gold standard" rescue agent ondansetron [23]. The institutional review board has reviewed the project and granted exemption for this retrospective chart review. Data was collected electronically at Hospital for Special Surgery from August 2018 to July 2019 and included adult patients (≥ 18 years) who were prescribed intravenous fosaprepitant 150 mg postoperatively. Data was obtained using a computerized data collection sheet, which collected additional patient information such as the use of other antiemetic medications during and after surgery. If further antiemetic's were needed after giving fosaprepitant as rescue, the medication and time of administration was documented. Nausea and vomiting were identified by utilizing multiple methods such as electronic medication message requests by nurses/prescribers, progress notes, chart reviews and PONV medication pyxis removal reports. A report of fosaprepitant use was generated from the electronic medical record which was MUE (Medication Use Evaluation) based to evaluate for study inclusion.

All patients were part of the same institutional PONV protocol which was consistent throughout all surgery types. Exceptions only occurred if significant drug-drug or drug-disease interactions existed. Prophylaxis for all included patients regardless of Apfel risk score consisted of one IV doses of both ondansetron 4 mg and dexamethasone 4 mg given intraoperatively, with dexamethasone given as high as 8 mg in spine cases when inflammation was a concern (lower dose or alternative for patients with DM). Additional prophylaxis agents were added in higher risk patients (≥ 3 risk factors as per Apfel risk score) or patients who had a prior history of PONV. The two additional agents used for prophylaxis were transdermal scopolamine placed preoperatively the evening before surgery (unless contraindicated) or a single dose of oral aprepitant (excluded in the study). Additionally, the protocol consisted of additional intraoperative methods to help reduce PONV risk. These include the use of regional anesthetics,

Table 1: Demographics.

Category	Relief (%)	No Relief (%)	p-value
Age			
<20 y	10 (91%)	1 (9%)	0.065
20-30 y	14 (88%)	2 (12%)	0.03
31-40 y	23 (82%)	5 (18%)	0.01
41-50 y	22 (69%)	10 (31%)	0.046
51-60 y	50 (74%)	18 (26%)	0.0005
61-70 y	74 (71%)	30 (29%)	0.0001
>70 y	93 (71%)	38 (29%)	<0.0001
Gender			
Males	103 (75%)	34 (25%)	0.100
Females	183 (74%)	63 (26%)	
BMI			
<25	79 (77%)	24 (23%)	0.0002
25-30	140 (77%)	41 (23%)	<0.0001
30-35	43 (74%)	15 (26%)	0.024
35-40	21 (60%)	14 (40%)	0.4334
>40	3 (50%)	3 (50%)	----------
History of PONV			
Yes	42 (58%)	30 (42%)	<0.0002
No	244 (78%)	67 (22%)	
Smoking status			
Yes	35 (67%)	17 (33%)	0.132
No	251 (76%)	80 (24%)	
Post-Op Opioids			
Yes	257 (76%)	80 (24%)	0.024
No	29 (63%)	17 (37%)	

avoidance of volatile anesthetics and opioid sparing techniques such as IV ketorolac, ketamine, and acetaminophen with precautions and contraindications taken into consideration. The postoperative rescue protocol contained agents that were written "as needed" and existed as part of an existing order-set. These agents included Ondansetron, Metoclopramide, Trimethobenzamide and Diphenhydramine. Alternative rescue agents that can be ordered separately are granisetron, prochlorperazine and promethazine.

When looking at the demographics, age played a significant role in the level of PONV relief (Table 1). The majority of patients observed in this study were above 60 years of age. The significance of relief (71-88%) was different across all age groups except in those under 20 years of age. When assessing gender, females would seem to have a higher incidence of PONV comprising more than double of the study population assessed (Table 1). A baseline gender assessment would be needed to support this claim as this may be a result of more females undergoing surgery during the assessment time frame. No difference existed between male and female in regards to relief. When observing BMI and PONV relief with fosaprepitant, patients with a BMI of 35 or lower seemed to benefit most (74-77%). Patients who did not have a history of PONV seemed to have had more relief than those with a PONV history (78% *vs.* 58%). When assessing the type of anesthesia given (general *vs.* regional) and relief with fosaprepitant, the proportions for both anesthesia types were the same in which fosaprepitant relief was not associated with anesthesia type (Table 2). Regional anesthesia consisted of neuraxial (n=181) and peripheral nerve blocks (n=30) in this review. Based on surgery types with sufficient sample size.

The primary endpoint of this study was the relief of emesis after fosaprepitant administration. This was obtained primarily through the pharmacist clinical interventions as well as utilizing chart reviews and progress notes. The clinical pharmacists were critical in the overall documentation and monitoring of patients who've received fosaprepitant. PONV was a focus within the clinical pharmacist team and placing fosaprepitant specific clinical interventions was a requirement. These interventions had information regarding the justification of fosaprepitant use and the level of emesis relief following administration. A pharmacist intervention was recorded for all patients who received fosaprepitant for rescue. These specific pharmacy interventions ware placed in the patient profile and were a result of the Pharmacy and Therapeutics committee's decision to track fosaprepitant cost and effectiveness as a PONV rescue agent.

Secondary endpoints were whether patients received an anti-emetic medication after fosaprepitant, and time after fosaprepitant administration when the anti-emetic was given. A safety evaluation was done in which the most common drug specific side effects consisted of extremity pain, fatigue and diarrhea.

Discrete variables are reported as frequencies and percentages. Analysis to test the strength of association of baseline variables was done with a two-sample test of proportions. A Chi-square test was utilized to compare fosaprepitant relief between genders. Logistic regression was used to compare odds of fosaprepitant relief between operative agents administered, reporting the crude Odds Ratio (cOR), Standard Error (SE), and 95% Confidence Interval (95% CI). Statistical significance was defined as $p \leq 0.05$. All analyses were performed with Stata, version 14.2 (StataCorp., College Station, TX).

Results

446 total patients were initially screened for inclusion in which 63 patients were excluded. Out of the 63 excluded patients, 51 patients received fosaprepitant within 6 h of another agent and 12 were chronic pain patients. 383 patient profiles were included/assessed in total and of the 383 patients who received fosaprepitant, 286 (74.9%) patients overall reported relief of emesis when fosaprepitant was used as a rescue agent. Of the 286 patients who obtained relief, 196 (69%) patients did not require another antiemetic medication afterwards. The remaining 90 (31%) patients who felt immediate relief from fosaprepitant but had to receive further antiemetic medication on an average of 13.65 h after fosaprepitant. The most common two agents in this study that failed for rescue prior to qualifying for fosaprepitant

Table 2: Anesthesia.

Category	Relief (%)	No Relief (%)	P-Value
Anesthesia Type			
General (n=172)	120 (70%)	52 (30%)	0.442
Regional (n=211)	166 (79%)	45 (21%)	
Anesthesia Time			
<1 h	7 (100%)	0	----------
1-2 h	35 (73%)	13 (27%)	0.01
2-3 h	141 (85%)	24 (15%)	<0.0001
>3 h	103 (63%)	60 (37%)	0.309

Table 3: Surgery.

Surgery Type	Relief (%)	No Relief (%)	p-value
Adult Reconstruction + Joint Replacement (n=165)	128 (78%)	37 (22%)	<0.0001
Trauma (n=4)	3 (75%)	1 (25%)	0.371
Sports Management and Shoulder (n=54)	44 (81%)	10 (19%)	0.0012
Pediatric Orthopedics (n=8)	5 (62.5%)	3 (37.5%)	0.352
Spine (n=125)	83 (66%)	42 (34%)	0.015
Hand and Upper Extremity (n=8)	7 (87.5%)	1 (12.5%)	0.090
Limb Lengthening (n=8)	7 (87.5%)	1 (12.5%)	0.090
Foot and Ankle (n=9)	7 (78%)	2 (22%)	0.141
Pain Management (n=2)	2 (100%)	0 (0%)	----------

were ondansetron and metoclopramide.

Demographics were categorized by age, gender, BMI, postoperative opioid use, as well as PONV and smoking history. Sports management and shoulder 81% (p=0.0012). Adult reconstruction and joint replacement 78% (<0.0001) and spine 66% (p=0.015). fosaprepitant showed significant PONV relief (Table 3). From a safety standpoint, we monitored patients and screened for fosaprepitant related adverse effects for a minimum of 24 h after administration. The most common adverse effects observed were extremity pain (n=26) at the fosaprepitant injection site, fatigue (n=19) and diarrhea (n=7).

Discussion

In this study, pain management protocols were similar throughout most of the surgical types. Multimodal analgesia, utilizing different mechanisms of action and targeting different pain pathways was a common practice to minimize opioid use. Most common combinations given included local anesthetics, NSAIDS, acetaminophen and opioids. Preoperative medications given may include oral acetaminophen 1 g, celecoxib 400 and gabapentin 300 mg (only for gabapentin tolerant patients). Intraoperative analgesia consists of peripheral nerve blocks, ketorolac (15 mg IV x 1 as clinically appropriate), acetaminophen during surgical closure (1 g IV x if PO not given preoperatively) and ketamine (IV up to 50 mg). Postoperative management consisted of resuming acetaminophen (1 g PO/IV q6h x 3 doses) and ketorolac (15 mg IV q6h x 3 doses) with the addition of oxycodone 5 mg to 10 mg po q3h prn and hydromorphone 0.5 mg IV q3h prn (rescue). Intravenous and Epidural Patient Controlled Analgesia (PCA) was commonly started postoperatively (depending on the procedure) and discontinued within a 24-h period. The infusion was programmable by the prescriber which contained a bolus feature given within a specified time frame and a basal rate if the patient required it.

Rescue agents are limited, especially when multiple agents are given intraoperatively. Typically, an agent of a different class should be given within 6 h from the last dose. As discussed earlier, 69% of patients didn't require further antiemetic rescue and the remaining 31% that did require additional relief, did so at an average of 13.65 h after fosaprepitant administration. This is still beneficial as ondansetron typically provides 6 h to 8 h of relief. With regards to PONV rescue medications, some of these agents also have limitations and restrictions which limit your options even further. Ondansetron may lead to QTc prolongation and discouraged with specific patients/medications. Ondansetron is the most popular medication for PONV and usually given intraoperatively (before the induction of anesthesia) and incorrectly re-challenged within the 6-h time frame. Dexamethasone may lead to hyperglycemia and used cautiously in diabetics. Metoclopramide has multiple drug interactions (Antidepressants, Antipsychotics, Anti-Parkinsonian medications etc.) making it less popular than other agents. Injectable promethazine and its safety concerns (inadvertent arterial injections and IV extravasation leading to serious tissue injuries and amputation) has led to many formulary removals [24].

Although not for rescue, scopolamine patch used for prevention should not be given within the elderly population as anticholinergics should always be avoided.

Upon data completion and assessment, fosaprepitant seemed to have potential in treatment of PONV in specific surgical types (Table 3). Without a comparator group it is unlikely that procedure type was a predictor or proved causation of fosaprepitant response but an association does exist. When comparing groups, these findings may suggest that fosaprepitant as a rescue is not age depended and we must take into consideration that the younger patients in this study were only a fraction of the total receiving fosaprepitant (reflects patient population in the orthopedic surgical setting). Although difficult to interpret in groups with a small sample size and retrospective in nature, a larger sample size may not likely make a significant difference for a single armed study since no matched historical control group exists and the possibility of a placebo affect must be considered. The Pharmacy and Therapeutics Committee's approval of fosaprepitant for PONV rescue at our institution was done so with conditions to monitor use. Although a prospective system utilizing pharmacy interventions were put in place for recording/tracking fosaprepitant use as well as monitoring efficacy and safety, the retrospective data collection can lead to observational bias and limited control of confounding factors. The retrospective nature of the study is a limitation and utilizing the electronic medical record to assess efficacy may lead to some inaccuracies. The assessment of 'efficacy' in a transient condition such as PONV is challenging without a comparator or control. Without this, it is not possible to draw any true conclusions about response to a given therapy. Further trials would benefit from utilizing different doses as well as alternate routes (oral aprepitant), to potentially optimize efficacy, safety and cost.

Conclusion

Due to the design of the present study, conclusions that can be made from the findings are somewhat limited and it is difficult

to assess the reliability of the findings presented. This retrospective chart review showed that the use of fosaprepitant as a rescue agent for postoperative nausea and vomiting in the orthopedic surgical setting yielded potential relief and was appropriate. A single 150 mg IV dose of fosaprepitant administered over 30 min to treat PONV (for patients who had a history of PONV or failed 2 antiemetic's postoperatively) was well tolerated and provided good relief of 8 h or more in the orthopedic surgical setting. A total of 169 (69%) of patients observed did not require additional emesis control after fosaprepitant administration and for the 90 (31%) patients that did, it was shown that fosaprepitant has the potential to prolong the need for further administration of antiemetic medications. More data is needed, a larger prospective randomized study with multiple surgical types to limit confounding factors and get a better understanding of fosaprepitant in different patient populations.

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